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EXHIBIT 1

Treatment Options

Treatment Options > Chemotherapy > Overview

Biological Response Modifiers

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Introduction

Biological response modifiers (BRMs) are another form of chemotherapy sometimes administered to cancer patients. They modify the relationship between the tumor and the patient by strengthening the patient's biological response to tumor cells. BRMs can be divided into three major categories according to mechanism of action:

1. agents that restore, augment, or modulate the patient's normal immunological mechanisms;
2. agents that have direct antitumor effects; and
3. agents that have other biologic effects, such as interference with a tumor cell's ability to metastasize or survive after metastasis, promotic of cell differentiation, or interference with neoplastic transformation in cells.

Scientists began studying BRMs in cancer therapy in the 1960s, labeling the treatment modality *immunotherapy*. After promising results in animal studies researchers initiated many large-scale clinical trials to stimulate cancer patients' immune systems using the bacterial agents *Bacillus Calmette-Guerl* (BCG) and *Corynebacterium parvum (C. parvum)*. The results of these trials were discouraging, so the research into immunotherapy as a possible modali for cancer treatment lost momentum.

Recent advances have prompted a renewed interest in BRMs, and today biological response modification is an important area in cancer research and treatment.

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Through Art is an exhibition by people whose lives have been touched by cancer.

Today's featured work:
Quell
by Bruce Pollock

Immune System: Background

The body's immune system mounts a coordinated combination of nonspecific and specific responses to foreign substances (e.g. microbes, and certain othe toxins, called *antigens*). Both physical injury and the presence of antigens ca invoke nonspecific host defenses. These defenses include physical barriers ar chemical factors, such as the skin and mucous membranes, acidic gastric secretions, and normal intestinal flora. The "inflammatory response" is anoth nonspecific host defense that serves to control the growth of microorganisms and prevent systemic infection.

Specific immune responses are elicited by the presence of an antigen. These reactions are characterized by a memory: following the initial exposure to an antigen, specific portions of the immune system produce memory cells that promote a more vigorous response to subsequent exposures to the same antigen. These specific memory responses are generally divided into *humoral* and *cell-mediated* immunity.

Humoral immunity refers to the immunity conferred by the B-lymphocyte cel produced by the lymph system. These lymphocytes, also called the *B-cells*, produce antibodies. Antibodies are small proteins that can deactivate antigen by a variety of mechanisms, usually by binding with them. Antibody-antigen interaction is specific: Only one type of antibody can interact and neutralize a specific type of antigen. This interaction then activates the "complement cascade," a system of proteins that "complements" antibody activity by destroying bacteria and helping the body rid itself of antibody/antigen complexes.

Cell-mediated immunity refers to the immunity conferred by the mutation of lymphocytes, which is thought to occur in the thymus gland. These lymphocytes, also called *T cells*, directly or indirectly destroy viruses, malignant cells, cells infected with intracellular organisms, and cells of grafte organs. Different types of T cells have different immune functions: *cytotoxic* cells directly destroy antigens; helper T cells activate the "humoral immune system" and cytotoxic T-cells; and suppressor T cells inhibit antibody production and other immune responses.

Other cells that are important in the immune response are *macrophages* and *natural killer (NK) cells*. Macrophages are white blood cells with a number of important functions. They bind to an antigen and "present" the antigen to undifferentiated cells (precursor cells); these, in turn, become activated and produce mature lymphocytes. Without this macrophage processing, the T an B cells could not respond to some types of antigens. NK cells are cytotoxic to tumor cells and virus-infected cells.

Many cells in the immune system produce chemicals that aid in regulating th immune response. These substances are referred to as mediators and broadl referred to as *cytokines*. Many cytokines are under study, to determine their effect on the immune system.

Types of BRM Therapy

A brief review of BRM agents currently being evaluated follows.

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Monoclonal Antibodies
The use of monoclonal antibodies (MoAbs) involves the development of speci antibodies directed against antigens located on the surface of tumor cells. Samples of the patient's tumor cells are taken and processed to reveal specif antibodies to the tumor-associated antigens. In order for this approach to work, a sufficient quantity of antigens unique to the tumor cells must be present. In addition, the tumor antigens must be sufficiently different from th antigens elaborated to by normal cells to provoke an antibody response.

The antibodies can be used either alone to kill cancer cells or as carriers of other substances used for either therapeutic or diagnostic purposes. For example, chemotherapeutic agents can be attached to monoclonal antibodies to deliver high concentrations of these toxic substances directly to the tumor cells. In theory, this approach is less toxic and more effective than conventional chemotherapy because it reduces the delivery of harmful agents to normal tissues is decreased.

Monoclonal antibodies can also be used for diagnostic purposes. They may be used to carry radioactive substances to cancer cells, thus pinpointing the location of metastases previously undetected by other methods.

Despite these uses, some monoclonal antibodies have limitations. Because some monoclonal antibodies may be made using mouse antibodies, they are, themselves, foreign proteins that often trigger an immune response; thus, they can be neutralized before any therapeutic effect occurs. In addition, monoclonals may lack specificity for tumor antigens; Tumor cell antigens ma not be different enough from those on normal cells to ensure only cancer cell destruction; studies have revealed that most monoclonal antibodies interact with antigens on both normal and cancer cells.

More recently, many monoclonal antibodies have been created which are onl derived from human proteins. Some are already FDA-approved and many others are in clinical trials, with approval imminent. In general, they have proven useful in treatment of hematologic malignancies and lymphoma. In addition, monoclonals are in development for use against solid tumors. All of these antibodies have multiple potential applications including nuclear imagir surgical mapping, and direct therapy in multiple settings (alone, in conjunctic with chemotherapy, for treatment of metastases, in adjuvant settings, in higl dose rates, etc.) In the future this field will most likely grow in importance in the war against cancer.

In the clinical setting, therapeutic monoclonal antibodies are usually given ov 4-6 hours by continuous intravenous infusion. Because of the risk of serious allergic reactions (particularly with the mouse antibodies), patients are premedicated with acetaminophen and an antihistamine and monitored closely. Emergency drugs are kept by the bedside. Potential side effects of monoclonal antibodies include dyspnea and mild wheezing, fever, chills, headache, rash, nausea, vomiting, tachycardia, and allergic reactions.

Research studies are currently underway using monoclonals for a variety of diseases, include T cell lymphoma, chronic and acute lymphocytic leukemia, melanoma, colorectal cancer, and neuroblastoma.

Interferons
Interferons (IFNs) are small proteins that inhibit viral replication and promot

the cellular (T-cell) immune response. Interferon use for cancer treatment w limited until the late 1970s, when technological advances enabled mass production of IFN.

There are currently three major types of IFNs: alpha, beta, and gamma. Eacl type has similar but distinctive capabilities for altering biological responses.

Alpha-IFN was the first BRM approved by the Food and Drug Administration (FDA) in 1986. Two different manufacturers have brands of this product available. Its main indication is for use in treatment of hepatitis C, but it is currently also indicated for use in the treatment of hairy cell leukemia and AIDS-associated Kaposi's sarcoma. It has also demonstrated therapeutic effectiveness against hematologic diseases such as low-grade Hodgkin's lymphoma, cutaneous T-cell lymphoma, multiple myeloma, and chronic myelogenous leukemia. It has also proven to be somewhat effective on some solid tumors, such as renal cell cancer. Beta-interferon is currently in use for treatment of multiple sclerosis.

Interferons may produce side effects of varying frequency and intensity depending on dose, schedule, route of administration, and the type of IFN. There is currently a "once per week" formulation of INF in late clinical trials which reduces the overall side effects experienced by patients. One of the most common side effects of IFN therapy is a flu-like syndrome. Symptoms include fever, chills, tachycardia, muscle aches, malaise, fatigue, and headaches. This reaction is extremely common during a patient's first exposure to IFN, but usually decreases in intensity with continued therapy.

Other common side effects to IFN include a decreased white blood cell count, anemia (with prolonged therapy), and decreased platelets. Gastrointestinal symptoms such as a loss of appetite, nausea, vomiting, and diarrhea may als be present. Central nervous system toxicities range from mild confusion and sleepiness to seizures. Acute kidney failure is rare, but can occur. Loss of hal may also be a problem.

Interferon can be administered by IV bolus or infusion, or intramuscular, subcutaneous, or intrathecal injection. It can also be given intranasally. Redness and irritation at the injection site may occur. Since IFN is often administered on an outpatient basis, it is essential that the patient and famil are taught the technique of administration and how to manage side effects.

Interleukin-2

Interleukin-2 (IL-2) is a substance produced by lymphocytes. In addition to being an essential factor for the growth of T cells, IL-2 augments various T-c functions and enhances NK cell function. IL-2 also activates *lymphokine-activated killer* (LAK) *cells*, which are a type of killer T cell produced when lymphocytes are incubated with IL-2. LAK cells destroy tumor cells and improve the recovery of immune function in certain immunodeficiency states Patients with renal cell cancer, melanoma, and non-Hodgkin's lymphoma hav demonstrated responses to IL-2 therapy.

The most severe toxicities result from IL-2's ability to increase capillary permeability. This may cause hypotension, ascites, generalized body edema, and pulmonary edema.

Chills and fever also frequently occur within a few hours after IL-2

administration. Headache, malaise, and other flu-like symptoms are also common. Gastrointestinal effects include nausea, vomiting, loss of appetite, diarrhea, and mucositis. Some liver dysfunction is common during therapy bu resolves once treatment is stopped. Central nervous system toxicity if manifested by lethargy, confusion, disorientation, and hallucination, anxiety, and sometimes depression. Although the effect of IL-2 on the kidneys is generally mild, renal failure can result if severe hypotension occurs. Hypotension, anemia, and a decrease in platelets are more likely with higher cumulative doses. Skin changes include redness, rash, pruritus, and occasionally skin desquamation.

Although many research studies with IL-2 require intensive supportive care i acute care settings, other current treatment regimens can be given on an outpatient basis. Patient education in these situations is especially important because patients must be alert to potential side effects that should be report immediately.

Colony Stimulating Factors

Colony stimulating factors (CSFs) are growth factors which mediate the proliferation, maturation, regulation, and activation of granulocytes, macrophages, lymphocytes, monocytes, erythrocytes, and platelets. Many types of CSFs have been produced synthetically. Some have been approved f use and some are in various stages of clinical trials. Generally, CSFs have be named for the major cell lineage they affect. Granulocyte-macrophage CSF (GM-CSF) affects both granulocyte and macrophage lineage; granulocyte CSI (G-CSF) targets only granulocytes. These two have been FDA-approved. The main indication is for treatment of neutropenic fevers. This has been studied multiple scenarios, including the prevention of neutropenic fevers primarily o secondarily, and for use in stem cell mobilization. Other colony stimulating factors include pleuripoletin IL-3, or multi-CSF, which affects early cell lineages, and macrophage CSF (M-CSF) targets macrophage production. Neumega is an IL-11 that induces platelet growth (and has FDA approval) an was hoped to limit the amounts of platelet transfusions patients may require. Unfortunately, the outcomes data has not demonstrated it to be as efficacious as originally hoped, and therefore is not often used. Other colony stimulating factors include thrombopoetin and platelet-derived growth factor (PDGF), which have been shown to induce antibodies which created platelet resistanc thus prompting their manufacturers to strongly consider removing from the market. Erythropoletin, which targets erythrocyte production, was approved the FDA in 1989 for use in anemia caused by end-stage renal disease (Epo (tm)). Another version, manufactured by Ortho Biotech (Procrit) is used to treat anemia related to cancer and cancer therapy as well and the fatigue which result.

GM-CSF and G-CSF have been administered by IV bolus, subcutaneously by daily injection, or by continuous IV infusion. G-CSF therapy has been associated with only minimal toxicity, mainly bone pain. GM-CSF produces more systemic toxicities, including fatigue, fever, muscle aches, anorexia, ra and diarrhea. Blood levels of alkaline phosphatase and aminotransferases ma also be increased.

Medical use of these growth factors is an important step in understanding an manipulating the immune system. Their efficacy in the treatment of congenit hematologic diseases and their ability to reduce neutropenia during cancer

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treatment, makes them important agents in the treatment armamentarium.

Tumor Necrosis Factor

Tumor necrosis factor (TNF) is a substance naturally secreted by macrophages. When activated by endotoxins, the macrophages release TNF, which then binds to receptors on cell membranes. Once bound to the cell membrane, TNF initiates cellular activity and is possibly cytotoxic to that cell.

TNF is in the early phases of clinical trials and has not yet demonstrated therapeutic effectiveness against malignant diseases. Side effects of TNF are similar to those experienced with interferon therapy, including a flu-like syndrome and soreness at the injection site. Fevers and chills are generally mild and disappear with subsequent doses of TNF.

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